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Calcium acetate, an effective phosphorus binder in patients with renal failure

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Calcium acetate, an effective phosphorus binder in patients with renal failure. Calcium salts are increasingly used as phosphorus binders in patients with chronic renal failure. Calcium carbonate is the principal salt presently utilized, however, other calcium salts may be more effective and safer phosphorus binders. Theoretical calculations, in vitro experiments, and in vivo studies in normal subjects have shown calcium acetate to be a more effective phosphorus binder than other calcium salts. This salt has not previously been studied in patients with chronic renal failure. We used a one-meal gastrointestinal balance technique to measure phosphorus absorption, calcium absorption and phosphorus binding in six patients with chronic renal failure. Calcium acetate was compared with calcium carbonate and placebo. Equivalent doses (50 mEq Ca^{++}) of calcium acetate bound more than twice as much phosphorus (106 ± 23 mg) as calcium carbonate (43 ± 39 mg) $P < 0.05$. When phosphorus binding was factored for calcium absorption, calcium acetate bound 0.44 mEq $HPO_4^=$/mEq absorbed Ca^{++} compared with 0.16 mEq $HPO_4^=$ bound/mEq Ca^{++} absorbed with calcium carbonate. More efficient phosphorus binding permits serum phosphorus concentration to be controlled with lower doses of calcium salts. The higher phosphorus binding/calcium absorption ratio coupled with a lower dose indicates that less calcium will be absorbed when calcium acetate is used for phosphorus control. Markedly positive calcium balance, hypercalcemia and ectopic calcification should be less likely to occur with this drug than other calcium salts.

Patients with chronic renal failure can absorb toxic quantities of aluminum when aluminum salts are ingested as phosphorus binders [1–8]. This relatively recent discovery has accelerated the search for alternative safe and effective, aluminum-free phosphorus binders. Calcium carbonate is the most widely used, non-aluminum phosphorus binding salt [9–12]. However, large doses of calcium carbonate are often necessary to achieve adequate control of serum phosphorus concentrations. The ingestion of such large quantities of calcium enhances its absorption and can result in hypercalcemia and ectopic calcification [10–13].

Theoretical calculations, using well-defined equilibrium constants, suggested that calcium acetate should be an effective phosphorus binder [14]. In vitro experiments confirmed these theoretical calculations [14]. Subsequent in vivo studies in normal subjects found calcium acetate to be a more potent phosphorus binder than either calcium carbonate or calcium citrate [14].

Calcium acetate has not previously been studied in patients with chronic renal failure. We used a one-meal gastrointestinal washout technique to measure gastrointestinal phosphorus and calcium absorption from the meal [15, 16]. We then compared phosphorus binding by calcium acetate with calcium carbonate and placebo. A randomized double-blind protocol was utilized.

Methods

Subjects

We studied six subjects with end-stage renal disease who received chronic maintenance hemodialysis (approximately 4 hrs, 3 times per week). Three subjects were men and three were women. Age range was 39 to 62 years, with a mean age of 52 years. Each patient was medically stable. Patient #3 (Table 1) had been previously treated for aluminum bone disease with desferoxamine. The drug was stopped six months prior to the initiation of this study. Patient #6 was receiving oral $1,25(OH)_2$ vitamin D_3, 0.75 μg/day. Patients were studied between dialysis days.

The study was approved by the Institutional Review Board for Human Protection of Baylor University Medical Center. All subjects were paid a fee for taking part in these experiments. Informed written consent was obtained from each subject.

Materials

Calcium salts were provided in gelatin capsules containing 500 mg of calcium acetate and 315 mg of calcium carbonate (each equivalent to 125 mg of elemental calcium per capsule). Placebo contained 540 mg of lactose. The capsules were manufactured by Lyne Laboratories of Stoughton, Massachusetts for Braintree Laboratories, of Braintree, Massachusetts, USA.

The meal consisted of 80 g of ground sirloin steak seasoned with salt and pepper, 30 g of swiss cheese, 100 g of french fried potatoes, and 250 ml water. Test meals were prepared each day in duplicate: one meal to be ingested by the subject and the other to be analyzed for phosphorus and calcium. On average, the meals contained 346 mg of phosphorus, and 201 mg of calcium. Ten g of polyethylene glycol (PEG) dissolved in the water was ingested with the meal and served as a nonabsorbed marker.

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Table 1. Patient demographics and serum chemistry

Patient	Age	Sex	Months on dialysis	Serum [Ca] *mg/dl* (nl 8.5–10.5)	Serum [P_i] *mg/dl* (nl 2.5–4.5)	Serum 1,25(OH) vit D *pg/ml* (nl 10–60)
1	54	F	5	10.1	4.9	≤8
2	47	F	126	7.9	4.9	≤5
3	55	F	111	11.6	7.6	≤5
4	62	M	59	8.8	5.2	≤5
5	41	F	37	10.3	2.2	≤5
6	39	M	15	10.2	7.2	≤9

The poorly-absorbed lavage fluid used in this study has been previously described [15]. It contained 40 mmol Na_2SO_4, 25 mmol NaCl, 20 mmol $NaHCO_3$, 10 mmol KCl and 80 mmol mannitol.

Procedure

The method used to measure calcium and phosphorus absorption from a single meal has been previously described [16]. Subjects reported to the laboratory on a nondialysis day after an eight hour fast. Blood was drawn for baseline analysis of phosphorus, calcium and $1,25(OH)_2$ vitamin D_3 on the first study day.

Each subject was studied on four separate test days: 1. fast; 2. meal plus placebo; 3. meal plus calcium acetate (1 g elemental calcium); 4. meal plus calcium carbonate (1 g elemental calcium). The test day sequence was randomized.

On each study day the gastrointestinal tract was thoroughly cleansed by lavage using the poorly absorbed solution. Four hours after this cleansing lavage, subjects ingested one-half of the total dose of calcium salt, or placebo, together with 100 ml of deionized water. This was immediately followed by the standard meal and then the remaining half dose of calcium salt or placebo. After a ten-hour absorption period, the GI tract was again lavaged to remove unabsorbed dietary constituents and calcium salt. The rectal effluent was quantitatively collected for measurement of calcium, phosphorus, and PEG. On the fast day, the procedure was identical except neither a meal nor calcium salt was ingested.

Duplicate meals, capsules and rectal effluent were analyzed for calcium by atomic absorption spectroscopy and for phosphorus by the method of Fiske and Subbarow [17]. PEG was analyzed by the method of Hyden [18]. Each specimen was analyzed in duplicate. $1,25(OH)_2$ vitamin D_3 levels were measured by Nichols Institute, San Juan Capestrano, California, USA.

Analysis and calculations

Net absorption of phosphorus is calculated using the following equation:

$$\text{Net phosphorus absorption} = \text{phosphorus ingested} - \left(\text{effluent phosphorus after meal} - \text{effluent phosphorus after fast}\right)$$

The rectal effluent collected after the fast contained that phosphorus which had moved down a concentration gradient into the initially phosphorus-free lavage fluid. Thus, it represented the amount of phosphorus in the effluent which was attributable to the lavage procedure itself. This quantity was then subtracted from the effluent phosphorus collected following a meal to calculate the amount of ingested phosphorus which had escaped absorption.

Phosphorus binding by each calcium salt was calculated using the following equation:

$$\text{Phosphorus binding} = \text{Phosphorus absorbed from meal ingested with placebo} - \text{Phosphorus absorbed from meal ingested with binding salt}$$

Calcium absorption from the meal and from the meal plus calcium salt was calculated using analogous equations except that calcium intake included both the calcium in the meal and that in the capsules.

To compare phosphorus binding potency of calcium salts the ratio phosphorus bound/calcium ingested was calculated. Each measurement was converted to milliequivalents so that comparable units were used. The major calcium-phosphate precipitate which forms in the intestine is probably $CaHPO_4$. Therefore, a phosphate valance of 2 was used. Milligrams of phosphorus are converted to milliequivalents of $HPO_4^=$ by the multiplication factor of (1 mmol/31mg) (2 mEq/mmol) = 0.0645 mEq/mg.

To compare salts on the basis of phosphorus bound per unit calcium absorbed, the ratio mEq $HPO_4^=$ bound/mEq Ca^{++} absorbed was calculated.

Results

Patient demographics, baseline serum calcium, inorganic phosphorus and $1,25(OH)_2$ vitamin D_3 levels are shown in Table 1. Although patient #6 was receiving oral $1,25(OH)_2$ vitamin D_3 0.75 μg/day, his serum level remained subnormal.

On each test day the rectal effluent collected after the second lavage was analyzed for PEG to determine whether the nonabsorbed dietary constituents were completely recovered. Combined PEG recovery for all studies was 100.5 ± 0.7% (mean ± SEM; range: 93 to 111%). This indicates that excellent recovery was achieved.

Phosphorus and calcium absorbed from the meal alone and the meal plus calcium salt are shown in Tables 2 and 3. When the meal was ingested with placebo the subject absorbed 181 ± 31 mg (mean ± SEM) of phosphorus or 53% of the ingested load. The subjects did not absorb calcium but instead showed net calcium secretion of 28 ± 28 mg.

When calcium carbonate (1 g, or 50 mEq, of elemental calcium) was administered with the meal, phosphorus absorption fell to 138 ± 21 mg or 40% of the ingested load. Therefore,

Table 2. Intake, effluent output and absorption of phosphorus in patients with chronic renal failure

	Fast	Placebo			$CaCO_3$			Ca acetate		
	Out	In	Out	Abs	In	Out	Abs	In	Out	Abs
					mg					
1	212	342	432	122	348	349	211	345	512	45
2	91	342	91	342	322	271	142	361	319	133
3	29	332	235	126	338	293	74	325	303	51
4	139	343	323	159	350	331	158	341	375	105
5	54	352	263	143	350	336	68	350	383	21
6	83	362	254	191	339	248	174	356	343	96
Mean	101	346	266	181	341	305	138	346	373	75
SEM	25	4	42	31	4	15	21	5	28	16

Abbreviations are: In, ingested; Out, recovered; Abs, absorbed.

Table 3. Intake, effluent output and absorption of calcium in patients with chronic renal failure

	Fast	Placebo			$CaCO_3$			Ca acetate		
	Out	In	Out	Abs	In	Out	Abs	In	Out	Abs
					mg					
1	171	202	536	−163	1209	1202	178	1218	1190	199
2	91	210	319	−18	1221	949	363	1226	956	361
3	51	208	319	50	1200	922	329	1192	980	263
4	115	177	276	16	1180	769	526	1189	844	460
5	61	193	301	−47	1176	796	441	1176	843	394
6	89	216	309	−4	1197	994	292	1212	1096	205
Mean	101	201	325	−28	1197	939	355	1202	985	314
SEM	16	5	42	28	6	59	46	7	52	41

Abbreviations are: In, ingested; Out, recovered; Abs, absorbed; (−) sign indicates net secretion.

calcium carbonate bound 43 mg of phosphorus (181 mg − 138 mg). Calcium absorption from the meal plus calcium carbonate was 355 ± 46 mg or 30% of the total ingested calcium load. The phosphorus binding ratios were 2.8 mEq $HPO_4^=$ bound/50 mEq Ca^{++} ingested or 0.06 mEq $HPO_4^=$ bound/mEq Ca^{++} ingested. Factoring phosphorus binding for calcium absorption shows 2.8 mEq $HPO_4^=$ are bound while 17.8 mEq Ca^{++} are absorbed yielding a ratio of 0.16 mEq $HPO_4^=$ bound/mEq Ca^{++} absorbed.

An equivalent quantity of calcium acetate ingested with the meal reduced phosphorus absorption to 75 ± 16 mg or 21.7% of the ingested load. Therefore, calcium acetate bound 106 mg of phosphorus (181 mg − 75 mg). This is significantly greater than the amount of phosphorus bound by calcium carbonate ($P < .05$; Fig. 1). Calcium absorption from the meal plus calcium acetate was 314 ± 41 mg or 26% of the ingested calcium load. Therefore, 6.9 mEq $HPO_4^=$ were bound by 50 mEq of ingested calcium yielding a ratio of 0.14 mEq $HPO_4^=$ bound/mEq calcium ingested. Factoring phosphorus binding for calcium absorption shows that 6.9 mEq $HPO_4^=$ were bound for 15.7 mEq calcium absorbed or 0.44 mEq $HPO_4^=$ bound/mEq Ca^{++} absorbed.

Discussion

Patients with chronic renal failure are usually vitamin D deficient and also develop resistance to the action of vitamin D. Vitamin D deficiency and resistance have greater effects on intestinal calcium absorption than intestinal phosphorus absorption. The active component of calcium absorption falls markedly so that calcium absorption from a normal diet may cease or calcium secretion may occur. In contrast, patients with vitamin D deficiency continue to absorb a large fraction of ingested phosphorus.

We have previously studied phosphorus and calcium absorption from a standard meal in normal subjects using the gastrointestinal washout technique [14]. When normal subjects ingested a cheeseburger and french fries meal, containing 342 mg of phosphorus and 214 mg of calcium, they absorbed 77% of the phosphorus load and 20% of the calcium load. Our subjects with renal failure, studied with an identical technique and similar meal, absorbed 53% of ingested phosphorus but showed net calcium secretion.

Patients with modest renal failure can continue to absorb a large fraction of ingested phosphorus and yet maintain balance because secondary hyperparathyroidism develops and increases renal phosphorus excretion. However, this mechanism becomes inadequate when renal failure becomes severe. Maintenance of phosphorus balance at this stage requires a major reduction of phosphorus intake and/or the use of phosphorus binders to decrease gastrointestinal phosphorus absorption.

Phosphorus binding has for many years been accomplished by the ingestion of aluminum-based binding salts. Recently the toxicity of aluminum binding salts has been identified [1–8]. Consequently, other metal salts have replaced aluminum as phosphorus binders. A variety of calcium and magnesium salts have been utilized. In this study, we compared phosphorus

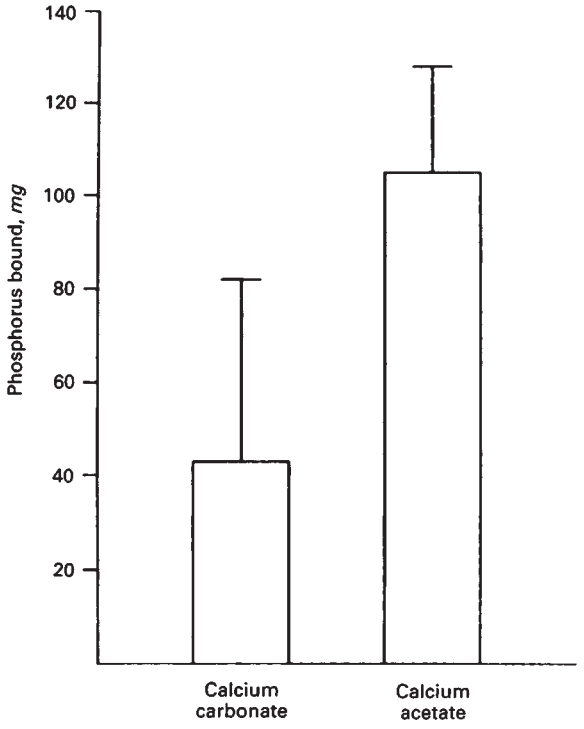

Fig. 1. *Phosphorus binding by calcium acetate and calcium carbonate.* Binding was calculated as the difference between phosphorus absorption with placebo and phosphorus absorption with each salt. One gm of elemental calcium (50 mEq) was ingested with the meal. Phosphorus binding by calcium acetate is significantly greater than binding by calcium carbonate ($P < 0.05$).

binding by calcium acetate with calcium carbonate in patients with chronic renal failure.

Calcium acetate (50 mEq elemental calcium) ingested with a meal containing about 345 mg of phosphorus bound more than twice as much phosphorus as calcium carbonate (106 mg vs. 43 mg). Converting to milliequivalent units and factoring phosphorus binding for ingested binder dose shows that 50 mEq of Ca^{++} ingested as the carbonate salt bound 2.8 mEq of phosphate (calculated as $HPO_4^{=}$). This yields a ratio of 0.06 mEq of $HPO_4^{=}$ bound/mEq of Ca^{++} ingested. Similar calculations for calcium acetate yield a ratio of 0.14 mEq $HPO_4^{=}$ bound/mEq Ca^{++} ingested. Both calcium salts are relatively inefficient binders. Although calcium acetate is more potent, only 14% of its potential phosphorus binding capacity is actually used to bind phosphorus (see below). Therefore, dietary phosphorus restriction remains a critical therapeutic cornerstone in patients with renal failure.

When subjects ingest low to normal amounts of calcium, intestinal calcium absorption is primarily accomplished via vitamin D dependent, or active, transport mechanisms. At such levels of calcium intake intestinal calcium absorption is linearly correlated with the serum 1,25 dihydroxyvitamin D levels [19]. However, when calcium intake is supplemented with ingested calcium salts, calcium absorption becomes less dependent on vitamin D activated mechanisms. When the luminal calcium concentration is increased to levels which saturate vitamin D dependent mechanisms, additional calcium absorption is accomplished by vitamin D independent, or passive, mechanisms. Therefore, despite low, or undetectable, vitamin D levels large amounts of calcium are absorbed when calcium supplements are administered.

The ingestion of 1 g of calcium, as the acetate salt, together with the meal resulted in the absorption of 314 mg of calcium, or 26% of the ingested load. Similarly, ingestion of 1 g of calcium as the carbonate salt together with the meal resulted in the absorption of 355 mg of calcium, or 30% of the ingested load.

The fraction of calcium which does not bind phosphorus, may combine with other dietary constituents, be absorbed, or be excreted in the stool in the form of the ingested salt. Systemic absorption of the salt can have either beneficial or toxic consequences. Patients with chronic renal failure are often in chronic net negative calcium balance and could therefore benefit from calcium supplementation. Indeed, dialysis solutions are usually designed to insure positive calcium balance during the dialytic period. However, excessive calcium absorption can produce hypercalcemia and ectopic calcification. The quantity of calcium absorbed in our study (26 to 30% of load) suggests that excessive calcium absorption may occur when these salts are used chronically. Therefore, calcium salts which are preferentially utilized to bind phosphorus and can be used in lower doses may be advantageous.

In view of the above considerations, calcium salts can be compared as phosphorus binders on the basis of quantity of phosphorus bound per unit of calcium absorbed. This calculation yields a ratio of 0.44 mEq of $HPO_4^{=}$ bound/mEq Ca^{++} absorbed when calcium acetate is used. This compares with 0.16 mEq $HPO_4^{=}$ bound/mEq Ca^{++} absorbed when calcium carbonate is utilized. On this basis, calcium acetate is almost three times more efficient than calcium carbonate. To achieve equal binding of phosphorus a smaller dose of calcium acetate than calcium carbonate can be used and less calcium will be absorbed.

Why is calcium acetate a more effective phosphorus binder than calcium carbonate? Calcium acetate is readily soluble in both acid and alkaline solutions. In vitro it rapidly and efficiently binds phosphorus in the pH range above 5 [14]. In contrast, calcium carbonate is much less soluble, requires an acid pH to dissolve and, in vitro, binds phosphorus much more slowly and incompletely than calcium acetate [14].

Achlorhydria is relatively common in patients with chronic renal failure [20]. In addition, inhibitors of gastric acid secretion and oral antacid preparations are often prescribed. If gastric pH is high then calcium carbonate may become less effective. Conversely, calcium acetate binds phosphorus even more effectively at higher pH.

To the extent the anion of the calcium salt is absorbed, important effects on acid-base balance will ensue. Absorption of carbonate from calcium carbonate directly alkalinizes the ECF. Absorption of acetate will also generate HCO_3^{-} when it is metabolized. Patients with chronic renal failure generally can tolerate large acetate loads which are infused during dialytic therapy with acetate-containing solutions. The potential acetate load delivered via calcium acetate ingestion would be much smaller.

Calcium chloride is another very soluble calcium salt with in vitro phosphorus binding characteristics similar to calcium acetate [14]. However, this salt has at least two important

disadvantages for clinical use. First it is a very astringent and unpalatable salt. Second, to the extent that the chloride is absorbed, it will produce systemic acidification [21, 22]. The calcium which remains in the intestinal lumen, in part, combines with HCO_3^- from pancreatic secretions, forming $CaCO_3$, while Cl^- is absorbed. Excretion of the relatively insoluble $CaCO_3$ into the stool represents systemic alkali loss and generates a metabolic acidosis.[1]

Calcium citrate is another relatively soluble calcium salt which has been used as a phosphorus binder [23, 24]. However, citrate forms soluble complexes with metal cations such as Ca^{++} and Al^{+++}. Formation of these soluble calcium citrate complexes decreases the availability of ionized calcium for reaction with phosphorus. Hence, in vitro calcium citrate dissolves rapidly but binds phosphorus poorly [14]. In addition, and of great clinical importance, citrate salts markedly increase intestinal aluminum absorption [25–27]. This may in part result from the formation of soluble aluminum citrate complexes which are more readily absorbed. Citrate, and other calcium chelators, may also open tight junctions between intestinal cells and thereby disrupt barriers to aluminum absorption [28, 29].

This study shows calcium acetate to be a more potent phosphorus binder than calcium carbonate in patients with renal failure. These results confirm and extend our findings in normal subjects [14]. Equal amounts of phosphorus are bound by smaller doses of calcium acetate compared with calcium carbonate. Consequently, the calcium load can be reduced and the potential toxicity of calcium salts decreased. Absorbed acetate is rapidly metabolized to HCO_3^- and should have no deleterious metabolic consequences. Acetate, unlike citrate, should not increase aluminum absorption. It is difficult to extrapolate chronic dose requirements from the results of this single dose study. Dose titration, using serial phosphorus measurements, will be required. Studies addressing this issue are in progress.

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[1] Although $CaCO_3$ also forms when other calcium salts are ingested, the net effect is the absorption of 1 mEq of potential HCO_3^- (i.e., acetate, citrate, etc.) for each mEq of $CO3^=$ bound by Ca^{++}. The acid-base effect of such an exchange is neutral.

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